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Obstetric cholestasis: outcome with active management

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Abstract

Objective: Conservative management of intrahepatic obstetric cholestasis is associated with a high stillbirth rate despite monitoring of fetal well-being with non-stress test and amniotic fluid volume assessment. Most cases of stillbirth are associated with meconium passage. We prospectively evaluated the effect of a management protocol inclusive of surveillance for presence of meconium and induction of labor at 37 weeks. *Study Design*: Between January 1989 and December 1997, all women with obstetric cholestasis underwent transcervical amnioscopy after 36 weeks for assessment of amniotic fluid color, in addition to standard monitoring of fetal well-being (semi-weekly non-stress test and amniotic fluid volume determinations). Amniocentesis for fetal lung maturity and amniotic fluid color assessment was performed before 36 weeks in severe cases. Labor was induced at 37 weeks or earlier in the presence of non-reassuring fetal testing, meconium, or severe maternal symptoms unresponsive to therapy with mature fetal lungs. The obstetric outcome of the group with cholestasis was compared with that of the general obstetric population at our Institution during the study period. The rate of fetal death in the study group was compared with that of series published within the last 20 years, which used expectancy and conventional monitoring of fetal well-being. Statistical analysis utilized Fisher's exact test, Chi-square, and Student's *t*-test with *P* value <0.05 or an odds ratio (OR) with 95% confidence interval (CI) not inclusive of the unity considered significant. *Results*: Obstetric cholestasis was diagnosed in 206/20,815 pregnant women (1%) at a median gestational age of 34 weeks (range 20–40). Delivery was prompted by non-reassuring fetal testing in four cases (2%). Meconium passage was documented in 33 cases (16%), in 11 of which before onset of labor and in 10 before 37 weeks. The rate of meconium passage before 37 weeks (17.9 versus 2.9%, OR = 7.3; 95% CI 3.3, 16.0) was significantly higher in obstetric cholestasis than in the general obstetric population, whereas the cesarean section rate was similar in the two groups (15.1 versus 16.0%, OR = 0.9; 95% CI 0.6, 1.4). The fetal death rate was significantly lower in the group managed with the current strategy than in the published series of obstetric cholestasis (0/218 versus 14/888, $P = 0.045$). *Conclusion*: In pregnancies complicated by obstetric cholestasis, a protocol inclusive of search for meconium and elective delivery at 37 weeks, in addition to standard monitoring of fetal well-being, can significantly reduce the stillbirth rate without increasing the cesarean delivery rate.

Keywords: Obstetric cholestasis; Meconium; Perinatal mortality

1. Introduction

Obstetric cholestasis is the most common liver disease of pregnancy, and is characterized by intrahepatic cholestasis triggered by environmental, infectious and hormonal factors in genetically predisposed women. This disorder is associated with increased risk of stillbirth and perinatal death [1]. The mechanism underlying cholestasis-associated stillbirths is unknown and conventional monitoring of fetal well-being does not predict most cases of fetal death, which may occur within 24 h of a reactive non-stress test [2–5]. Indeed, most stillbirths are not preceded by signs of chronic hypoxia, such as oligohydramnios or fetal growth restriction, or by acute fetal hypoxemia, as manifested by fetal heart rate changes. Interestingly, meconium passage has been reported in 86% of cholestasis-associated fetal deaths [3,6–9]. The mechanism underlying such association has not been elucidated. Most fetal deaths occur towards the end of pregnancy, and some series suggest an association between severity of maternal symptoms and poor fetal outcome [2].

The aim of this study was to evaluate whether a management strategy inclusive of search for presence of meconium and elective delivery at 37 weeks, in addition to standard monitoring of fetal well-being, could decrease the stillbirth rate in obstetric cholestasis compared with that of series published in the last 20 years.

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2. Materials and methods

During the period January 1989 to December 1997 all pregnant women with a diagnosis of obstetric cholestasis at our Department of Obstetrics and Gynecology were prospectively followed with a consistent protocol. The diagnosis of obstetric cholestasis was made in the presence of severe generalized pruritus with onset during the second or third trimester of pregnancy, persisting up to the time of delivery and disappearing after delivery, without skin or medical conditions known to be associated with pruritus [7]. The diagnosis was supported by demonstrating an elevation of serum aspartate aminotransferase, alanine aminotransferase, and/or bile acids levels. Pruritus was graded semi-quantitatively as grade 1, occasional; grade 2, daily intermittent with preponderance of asymptomatic periods; grade 3, daily intermittent with preponderance of symptomatic periods; and grade 4, persistent, day and night. The management protocol consisted of serial evaluation of serum liver function tests and monitoring of fetal well-being with semi-weekly non-stress tests and amniotic fluid volume determinations starting at fetal viability. A biophysical profile was performed if non-stress test was non-reactive. Given the prognostic significance of the presence of meconium-tinged amniotic fluid in obstetric cholestasis, amniotic fluid color was assessed weekly beginning at 36 weeks using transcervical amnioscopy, if the cervix was patent to the amnioscope, or amniocentesis. In addition, because clinical severity of cholestasis has been correlated with rate of fetal distress, amniocentesis was performed before 36 weeks' gestation to assess the color of amniotic fluid and fetal lung maturity in women with severe pruritus and serum transaminase levels above 300 mg/dl. Presence of meconium was considered by itself an indication for delivery. Patients were delivered at 37 weeks or at the time of diagnosis, if after 37 weeks. In the presence of obstetric complications, non-reassuring fetal testing, or severe maternal symptoms unresponsive to therapy and with mature fetal lungs delivery was expedited independently of gestational age. Fetal growth restriction was defined as an abdominal circumference below the 10th centile for local standards. Fetal lung maturity was assessed at 37 weeks only in the presence of diabetes mellitus (using an L/S ratio >3 to indicate maturity), or uncertain gestational age (using an L/S ratio >2 to indicate maturity). If fetal lungs were not mature and the amniotic fluid was clear, amniocentesis was repeated at weekly intervals until maturity was documented. The need for treatment, because of severe symptomatology or elevated serum levels of liver function tests, was decided in consultation with hepatologists. The therapeutic agents used were cholestiramine 9 g per day, *S*-adenosyl-L-methionine 500 mg twice daily or ursodeoxycholic acid 300 mg twice daily. Follow-up assessment of serum liver function tests was obtained 1 and 3 months after delivery.

The obstetric outcome of women with obstetric cholestasis was compared with that of the general obstetric population during the study period using Chi-square or Student's *t*-test, where appropriate, with a two-tailed P value <0.05 or an odds ratio (OR) with 95% confidence interval (CI) not inclusive of the unity considered statistically significant. To establish whether our management strategy significantly decreased the fetal death rate compared with expectant management with conventional fetal monitoring, we conducted a MEDLINE search (National Library of Medicine) for reports published in the English literature on obstetric cholestasis. To limit the confounding effects of changes of fetal monitoring techniques, we limited the search to series conducted between 1980 and 2000. The reference lists of all identified articles were examined to find additional relevant studies. Case reports or series with 10 or less cases, series originated from referral hepatology services, and those which did not provide information on obstetric management were excluded. To the list we added a historical cohort from our own hospital from 1984 to 1989 managed expectantly with non-stress tests alone [10]. The fetal death rate in the current study group was compared with that of the series fulfilling the above inclusion criteria using Fisher's exact test with a one-tailed $P < 0.05$ considered significant.

3. Results

During the study period, obstetric cholestasis was diagnosed in 206/20,815 pregnant women (1%), including 194 singleton and 12 twin pregnancies. Table 1 displays the demographic and obstetric characteristics of the study population. The median (range) highest serum aspartate aminotransferase after diagnosis was 87 mg/dl (11–1127, n.v. 8–41 mg/dl), serum alanine aminotransferase was 159 mg/dl (8–1734, n.v. 8–41 mg/dl), and bile acids level 16.5 μmol/l (0.6–200, n.v. <6 μmol/l). In 26 cases the serum bilirubin level was above the threshold of normality (1.2 mg/dl). Gestational age at diagnosis was less than 34 weeks in 76 (37%) and less than 37 weeks in 173 (84%) women. Treatment was required in 35 patients, and it included cholestiramine ($n = 19$), ursodeoxycholic acid ($n = 8$), and *S*-adenosyl-L-methionine ($n = 8$).

Table 1
Demographic and obstetric characteristics of the population with gestational cholestasis

	No. (%) or median (range)
Maternal age (years)	30 (20–45)
Gestational age at diagnosis (weeks)	34 (20–40)
Nulliparity	142/206 (69%)
History of gestational cholestasis	36/64 (56%)
Multiple gestation	12/206 (6%)
Treatment required	35/206
Pruritus grading	
1	22 (11%)
2	112 (54%)
3	54 (26%)
4	18 (9%)

Table 2
Indications for preterm delivery in women with gestational cholestasis

	No. (%)
Spontaneous preterm labor	9/206 (4.3%)
Indicated preterm delivery	47/206 (22.8%)
Meconium-stained amniotic fluid	10
Fetal growth restriction	5
Severe cholestasis	28
Non-reassuring fetal testing	3
Fetal anomaly with polyhydramnios	1

The rate of delivery at less than 37 weeks' gestation was 27.2% (56/206), which was significantly higher than in the general obstetric population (9.0% or 1873/20,815; OR = 3.8; 95% CI 2.7, 5.2). Table 2 shows the causes of preterm delivery in the study population. Amniocentesis for amniotic fluid color determination was performed in 35/206 cases (17.0%), and meconium was detected in 3 (8.6%) of them, at 31.6, 32.5, and 36.6 weeks' gestation. Amnioscopy led to the detection of meconium in seven additional cases before 37 weeks, yielding a rate of meconium passage before 37 weeks of 17.9% (10/56). This rate was significantly higher than that of our general obstetric population at less than 37 weeks during the same period (2.9%, or 54/1873; OR = 7.3; 95% CI 3.3, 16.0). In 28 women, preterm delivery was induced despite clear amniotic fluid and reassuring fetal testing because of severe maternal symptoms with lack of response to treatment, as well as worsening laboratory test results. The clinical symptomatology and laboratory abnormalities resolved by the first post-partum visit in all women.

The overall rate of meconium passage was 15.1% (33/206), including 11 cases before onset of labor and 22 during labor or at the time of cesarean delivery. Cases of obstetric cholestasis associated with meconium passage had similar severity as those without it (mean ± S.D. highest serum aspartate aminotransferase 93 ± 77 versus 130 ± 128 mg/dl, $P = 0.1$; serum alanine aminotransferase 154 ± 139 versus 225 ± 225 mg/dl, $P = 0.09$; bile acids level 27.0 ± 1.9 versus 24.0 ± 25.3 μmol/l, $P = 0.7$; and bilirubin 0.72 ± 0.38 versus 0.85 ± 0.50 mg/dl, $P = 0.2$). Similarly, there was no association between meconium passage and rate of oligohydramnios, defined as the largest pocket of amniotic fluid <2 cm × 2 cm (6/185 cases with clear amniotic fluid versus 1/33 with meconium-stained fluid, $P = 0.7$), or small for gestational age, defined as birth weight below 10th centile (11/185 cases with clear amniotic fluid versus 4/33 with meconium-stained fluid, $P = 0.2$). There was no case of meconium aspiration syndrome.

Median (range) gestational age at delivery among women with cholestasis was 37.4 weeks (30.3–41.3). Labor was induced in 146 (71%) women, and resulted in 31 cesarean deliveries for failed induction ($n = 10$), fetal distress ($n = 11$), dystocia ($n = 3$), and other indications ($n = 7$). In two cases the Apgar score at 5 min was below 7. The only infant with umbilical artery acidemia (pH = 7.06) had congenital cystic adenomatoid malformation of the lung and polyhydramnios, required corrective surgery in the neonatal period, and did well post-operatively. Two additional infants had congenital malformations (an aneurysm of the vein of Galen and a structural cardiac malformation). There were no differences in rates of cesarean delivery (15.1 versus 16.0%, OR = 0.9; 95% CI 0.6, 1.4), preterm delivery at <37 weeks (27.2 versus 9.0%, OR = 3.8; 95% CI 2.7, 5.2), or birth weight below 10th centile (6.9 versus 8.0%, OR = 0.6; 95% CI 0.3, 1.2) in women with obstetric cholestasis compared with the general obstetric population during the study period.

Table 3
Rates of stillbirths in published series of obstetric cholestasis managed expectantly

Reference	Total fetuses	Stillbirths	Rate/1000
[7]	101	1	9.9
[3]	86	2	23.2
[8]	328	4	12.2
Roger (1994)	23	1	43.5
[9]	79	2	25.3
Bacq (1997)	61	1	16.4
[2]	133	1	7.5
Total	888	14	15.8

Table 3 displays the published series which fulfilled our inclusion criteria, as well as the historical cohort from our own hospital from 1984 to 1989 managed expectantly with non-stress tests alone [10]. The stillbirth rate in our current population was significantly lower than in the cumulative series (0/218 versus 14/888, $P = 0.045$).

4. Comment

The risk of fetal mortality associated with gestational cholestasis is considerable [1] and traditional monitoring of fetal well-being has not been shown to prevent cholestasis-associated stillbirths. Even series in which patients with gestational cholestasis were hospitalized and underwent daily fetal monitoring reported cases of stillbirth with reassuring fetal testing as recently as 7 h before fetal death [4,9]. Our experience represents one of the largest series ever published, and it contains predominantly severe cases, as documented by the low gestational age at diagnosis (before 37 weeks in 84% of cases) and need for therapy (17%). The favorable outcome suggests that the risk of stillbirth with obstetric cholestasis can be significantly decreased by means of a search for presence of meconium and elective delivery at 37 weeks or earlier in the presence of meconium, non-reassuring fetal testing, or severe disease. Implementation of our strategy was associated with an increase in the rate of induction of labor and delivery before 37 weeks compared with the general obstetric population, but no difference in cesarean delivery rate.

It is difficult to discern which of the individual components of our protocol was responsible for the good perinatal outcome. In our series an immediate cesarean delivery was prompted in three cases by the presence of non-reassuring non-stress test. This underscores that traditional fetal testing has a modest but undeniable ability to predict some cases of fetal compromise associated with obstetric cholestasis. Our protocol emphasized search for presence of meconium because meconium passage is a reliable indicator of impending fetal death. Indeed, a review of the series which reported the rate of meconium-stained amniotic fluid in cases of fetal deaths associated with obstetric cholestasis reveals that meconium passage precedes fetal death in 86% (12/14) of cases [3,6–9]. Such rate is significantly higher than that of meconium passage associated with fetal death in our general obstetric population during the study period (23.3%, or 14/60) ($P < 0.0001$). Even though we did not observe any fetal death, the rate of meconium passage in our population with obstetric cholestasis was significantly higher than expected. Among cases delivered before 37 weeks, the rate of meconium-stained amniotic fluid was more than seven-fold higher in obstetric cholestasis than in our general obstetric population. Passage of meconium with obstetric cholestasis is not associated with a decrease in amniotic fluid volume or a higher rate of fetal growth restriction. This observation suggests that meconium passage with cholestasis is not secondary to chronic fetal hypoxia or placental dysfunction. Similarly, we found no association between meconium passage and laboratory evidence of severity of disease. Placental intervillous perfusion is not significantly different between cholestasis patients and controls [11]. Given the association between fetal death and meconium-stained amniotic fluid in obstetric cholestasis, further studies of the factors associated with meconium passage may provide clues to understand the pathogenic mechanism underlying fetal death in cholestasis.

In summary, in a population of predominantly severe obstetric cholestasis, a management strategy inclusive of search for presence of meconium and induction of labor at 37 weeks or earlier in the presence of meconium, non-reassuring fetal testing or severe disease reduces the risk of fetal death without a significant increase in cesarean delivery rate. Implementation of our strategy is therefore recommended until future studies provide clues on the pathogenesis of cholestasis-associated fetal death, and establish whether treatment can decrease the rate of cholestasis-related complications.

References

[1] Fagan EA. Diseases of the liver, biliary system, and pancreas. In: Creasy RK, Resnik R, editors. Maternal fetal medicine. Philadelphia: Saunders, 1999. p. 1054–81.
[2] Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 1984;22:91–4.
[3] Fisk NM, Storey GNB. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol 1988;95:1137–43.
[4] Londero F, San Marco L. Intrahepatic cholestasis of pregnancy: are we really able to predict fetal outcome? Am J Obstet Gynecol 1997;177:1274.
[5] Matos A, Bernardes J, Ayres-de-Campos D, Patricio B. Antepartum fetal cerebral hemorrhage not predicted by current surveillance methods in cholestasis of pregnancy. Obstet Gynecol 1997;89:803–4.
[6] Reid R, Ivey KJ, Rencoret RH, Storey B. Fetal complications of obstetric cholestasis. Br Med J 1976;1:870–2.
[7] Berg B, Helm G, Petersohn L, Tryding N. Cholestasis of pregnancy: clinical and laboratory studies. Acta Obstet Gynecol Scand 1986;65:107–13.
[8] Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato S, Parer JT, Germain AM. Intrahepatic cholestasis of pregnancy. A retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994;170:890–5.
[9] Alsulyman OM, Ouzounian JG, Ames-Castro M, Goodwin TM. Intrahepatic cholestasis of pregnancy: perinatal outcome with expectant management. Am J Obstet Gynecol 1996;175:957–60.
[10] Roncaglia N, Trio D, Roffi L, Bonacina MC, Pasta F. Colestasi intraepatica gravidica: incidenza, decorso, complicanze. Ann Ost Gin Med Perin 1991;CXII:146–51.
[11] Kaar K, Jouppila P, Kuikka J, Luotola H, Toivanen J, Rekonen A. Intervillous blood flow in normal and complicated late pregnancy measured by means of intravenous ^{155}Xe method. Acta Obstet Gynecol Scand 1980;59:7–10.